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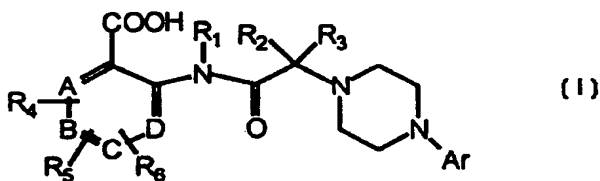
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 295/15, A61K 31/495		A1	(11) International Publication Number: WO 99/64407
			(43) International Publication Date: 16 December 1999 (16.12.99)
<p>(21) International Application Number: PCT/EP98/03431</p> <p>(22) International Filing Date: 8 June 1998 (08.06.98)</p> <p>(71) Applicant: MERCK PATENT GMBH [DE/DE]; D-64271 Darmstadt (DE).</p> <p>(71)(72) Applicant and Inventor: MOINET, Gérard [FR/FR]; 15, rue Lamartine, F-91400 Orsay (FR).</p> <p>(72) Inventors: BOTTON, Gérard; 9 bis, rue du Haras, F-78530 Buc (FR). PATEREAU, Gérard; 28, rue d'Aven, F-78310 Maurepas (FR). DOARE, Liliane; 33, avenue Marmont, F-91170 Viry-Châtillon (FR). KERGOAT, Micheline; 5, Villa des Bois, F-91440 Bures-sur-Yvette (FR). MESANGEAU, Didier; 5, rue Auguste Renoir, F-78380 Combs-la-Ville (FR). BIERER, Donald, D.; 880 Campus Drive No. 122, Daly City, CA 94015 (US).</p> <p>(74) Common Representative: MERCK PATENT GMBH; D-64271 Darmstadt (DE).</p>			<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>

(54) Title: α -(1-PIPERAZINYL)ACETAMIDO ARENECARBOXYLIC ACID DERIVATIVES AS ANTIDIABETIC AGENTS



(57) Abstract

The invention relates to compounds of general formula (I). These compounds are useful in the treatment of diabetes.

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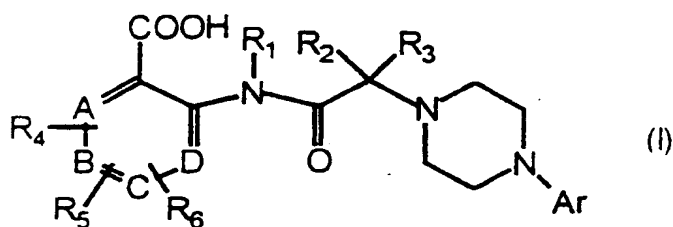
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α -(1-PIPERAZINYL)ACETAMIDO ARENECARBOXYLIC ACID DERIVATIVES AS ANTIDIABETIC AGENTS

The present invention relates to new α -(1-piperazinyl)acetamido
 5 arenecarboxylic acid derivatives which are useful in the treatment of diabetes.

The subject of the present invention is thus compounds of general
 formula (I):



in which:

Ar is selected from

- a mono-, bi- or tricyclic aryl group having from 6 to 14 carbon
 atoms,

- a heteroaromatic group selected from the pyridyl, pyrimidinyl,
 pyrrolyl, furyl, thienyl, quinolyl, indolyl, benzothienyl, benzofuryl, benzopyranyl,
 benzothiopyranyl, dibenzofuryl, carbazolyl and benzothiazinyl groups,

it being possible for the Ar group to carry 1 to 3 substituents
 selected from a C₁-C₈ alkyl, (C₃-C₈)cycloalkyl(C₁-C₆)alkyl, C₁-C₈ alkoxy, (C₃-
 C₈)cycloalkyloxy(C₁-C₆)alkyl, (C₃-C₈)cycloalkyl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₃-
 C₈)cycloalkyloxy, (C₃-C₈)cycloalkyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, C₆-C₁₄
 aryl, C₆-C₁₄ heteroaryl, (C₆-C₁₄)heteroaryl(C₁-C₆)alkyl, (C₆-C₁₄)aryl(C₁-C₆)alkyl,
 (C₆-C₁₄)aryl(C₁-C₆)alkyl(C₆-C₁₄)aryl, (C₆-C₁₄)aryloxy, (C₆-C₁₄)aryloxy(C₁-C₆)alkyl,
 (C₆-C₁₄)aryl(C₁-C₆)alkyloxy or (C₆-C₁₄)aryl(C₁-C₆)alkyloxy(C₁-C₆)alkyl group, a
 25 halogen, a trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, nitro, amino,
 carboxyl, (C₁-C₆)alkoxycarbonyl, carbamoyl, (C₁-C₈)alkylthio, (C₁-
 C₈)alkylsulphinyl, (C₁-C₈)alkylsulphonyl, sulphoamino, (C₁-

C₈)alkylsulphonylamino, sulphamoyl or (C₁-C₈)alkylcarbonylamino group, or two of these substituents forming a methylenedioxy group,

the 4-carboxyphenyl and substituted 4-carboxyphenyl groups being excluded from the definition of Ar,

5 R₁, R₂ and R₃ are selected, independently of one another, from:

- a hydrogen atom,
- a C₁-C₈ alkyl or (C₁-C₆)alkoxy(C₁-C₆)alkyl group,
- a cycloalkyl group containing from 3 to 8 carbon atoms, a (C₃-C₈)cycloalkyl(C₁-C₆)alkyl group or a (C₃-C₈)cycloalkyloxy(C₁-C₆)alkyl or (C₃-C₈)cycloalkyl(C₁-C₆)alkoxy(C₁-C₆)alkyl group,
- a C₆-C₁₄ aryl, C₆-C₁₄ heteroaryl, (C₆-C₁₄)heteroaryl(C₁-C₆)alkyl, (C₆-C₁₄)aryl(C₁-C₆)alkyl, (C₆-C₁₄)aryl(C₁-C₆)alkyl(C₆-C₁₄)aryl, (C₆-C₁₄)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl or (C₆-C₁₄)aryloxy(C₁-C₆)alkyl group,

15 A, B, C and D are =CH- groups, it being possible for one or two of them also to be a nitrogen atom,

R₄, R₅ and R₆ are selected, independently of one another, from:

- a hydrogen atom,
- a C₁-C₈ alkyl, (C₃-C₈)cycloalkyl(C₁-C₆)alkyl, C₁-C₈ alkoxy, (C₃-C₈)cycloalkyloxy(C₁-C₆)alkyl, (C₃-C₈)cycloalkyloxy, (C₃-C₈)cycloalkyl(C₁-C₆)alkoxy, (C₃-C₈)cycloalkyl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, C₆-C₁₄ aryl, (C₆-C₁₄)aryl(C₁-C₆)alkyl, (C₆-C₁₄)aryl(C₁-C₆)alkyl(C₆-C₁₄)aryl, (C₆-C₁₄)aryloxy, (C₆-C₁₄)aryloxy(C₁-C₆)alkyl, (C₆-C₁₄)aryl(C₁-C₆)alkoxy or (C₆-C₁₄)aryl(C₁-C₆)alkyloxy(C₁-C₆)alkyl group, a halogen or a trifluoromethyl, trifluoromethoxy, cyano, carboxyl, hydroxyl, nitro, amino, (C₁-C₆)alkoxycarbonyl, carbamoyl, (C₁-C₆)alkylthio, (C₁-C₈)alkylsulphinyl, (C₁-C₈)alkylsulphonyl, sulphoamino, (C₁-C₈)alkylsulphonylamino, sulphamoyl or (C₁-C₈)alkylcarbonylamino group, it being possible for two of these groups to form a methylenedioxy group or a phenyl ring condensed with the ring to which they are attached,
- 30 it being possible for the various aryl groups to be themselves substituted by 1 to 3 substituents selected from a C₁-C₈ alkyl or C₁-C₈ alkoxy group, a halogen or a trifluoromethyl, trifluoromethoxy, hydroxyl, nitro and amino group,

their solvates and their pharmaceutically acceptable salts.

Mention may be made, as an example of the aryl group, of the phenyl, α -naphthyl, β -naphthyl and fluorenyl groups.

The C₁-C₈ alkyl groups can be linear or branched. Mention may be made, as examples, of the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl and pentyl groups.

The C₁-C₈ alkoxy groups can likewise be linear or branched. Mention may be made, as examples, of the methoxy, ethoxy, propoxy, isopropoxy, butoxy and isobutoxy groups.

The halogens can be selected from fluorine, chlorine, bromine and iodine.

The heteroaryl groups in the definition of R₁, R₂ and R₃ may be defined in particular as defined for the heteroaromatic groups in the definition of Ar.

The invention also relates to the tautomeric forms and to the enantiomers, diastereoisomers and epimers of the compounds of general formula (I).

The compounds of general formula (I) possess a carboxylic acid functional group and can be salified, then existing in the form of salts with bases.

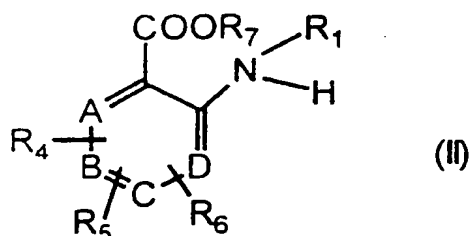
Examples of salts with bases of the compounds of general formula (I) include the pharmacologically acceptable salts, such as the sodium salts, potassium salts, calcium salts and other salts of the same type.

The compounds of general formula (I) can also be salified with amines in order to form pharmaceutically acceptable salts. By way of example, the compounds of general formula (I) could be salified with glucamine, N-methylglucamine, N,N-dimethylglucamine, ethanolamine, morpholine, N-methylmorpholine or lysine.

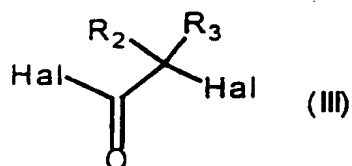
The compounds of general formula (I) possess basic nitrogen atoms and can be monosalified or disalified with inorganic or organic acids. Examples of salts with acids of the compounds of general formula (I) include the pharmacologically acceptable salts, such as, and non-exhaustively, the hydrochloride, the hydrobromide, the sulphate, the succinate, maleate, fumarate,

malate or tartrate and the sulphonates, such as the methanesulphonate, the benzenesulphonate or the toluenesulphonate.

The invention also relates to a process for the preparation of the compounds of general formula (I). A preparation process according to the invention comprises the reaction of an aromatic amine of general formula (II):

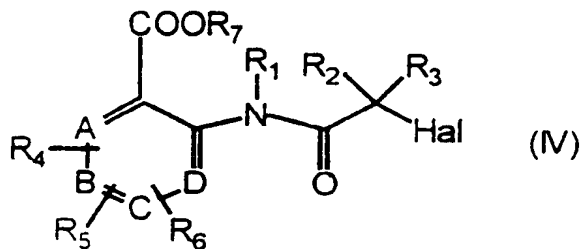


in which A, B, C, D, R₁, R₄, R₅ and R₆ are as defined above and R₇ is a hydrogen atom, a C₁-C₆ alkyl group or a benzyl group, with a haloacyl halide of general formula (III):



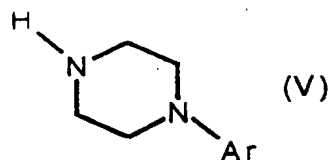
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in which R₂ and R₃ are as defined above,
Hal represents a chlorine or bromine atom,
in order to form a compound of general formula (IV):

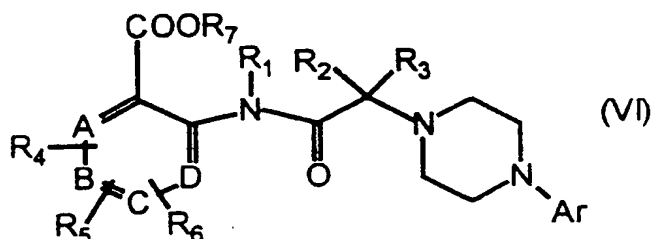


15 in which A, B, C, D, R₁, R₂, R₃, R₄, R₅, R₆, R₇ and Hal are as defined above, and the reaction of the compound of general formula (IV) with a compound of general formula (V):

5



in which Ar is as defined above,
in the presence of a basic agent, such as triethylamine, in order to form the compound of general formula (VI):



5

in which Ar, A, B, C, D, R₁, R₂, R₃, R₄, R₅, R₆ and R₇ are as defined above.

In the case where R₇ is an alkyl group, the compound of general formula (VI) can be hydrolysed by conventional acidic or basic means in order to give the compound of general formula (I).

In the case where R₇ is a benzyl group, the compound of general formula (VI) can be hydrogenolysed in the presence of a catalyst, such as palladium-on-charcoal, in order to give the compound of general formula (I).

The compounds of formulae (II) and (V) are known compounds or can be prepared according to known processes.

Thus, compounds of formula (II) are described in Organic Preparation and Procedures International, 13, 189, 1981.

The compounds of formula (V) can be prepared as described by R. Ratouis et al. (J. Med. Chem., 8, 104, 1965) or by Prelog et al. (Collection Czechoslov. Chem. Communications, 6, 211, 1934).

By way of example, the compound (VI), in which R₇ is an alkyl group, can be hydrolysed in the presence of a basic agent, such as dilute sodium hydroxide.

The enantiomers of the compounds of formula (I) can be separated by successive recrystallization of the salt of the acid (I) with an optically active base in solvents such as acetone, ethyl acetate or isopropanol and then displacement from the salt into an optically active acid by an inorganic or organic acid, according to a conventional method.

The compounds according to the present invention can be used in the treatment of diabetes, in particular of non-insulin-dependent diabetes, because of their hypoglycaemic effect and of their absence of toxicity at the active doses.

Another subject of the present invention is thus pharmaceutical compositions comprising an effective amount of a compound according to the invention.

The pharmaceutical compositions according to the invention can be presented in forms intended for parenteral, oral, rectal, permucosal or percutaneous administration.

They will thus be presented in the form of injectable solutions or suspensions, or multi-dose containers, in the form of uncoated or coated tablets, of sugar-coated tablets, of capsules, including hard gelatin capsules, of pills, of cachets, of powders, of suppositories or of rectal capsules, of solutions or of suspensions, for percutaneous use in a polar solvent or for permucosal use.

The excipients which are suitable for such administrations are derivatives of cellulose or microcrystalline cellulose, alkaline-earth metal carbonates, magnesium phosphate, starches, modified starches or lactose for the solid forms.

Cocoa butter or polyethylene glycol stearates are the preferred excipients for rectal use.

Water, aqueous solutions, physiological solution or isotonic solutions are the most conveniently used vehicles for parenteral use.

The dosage can vary within wide limits depending on the therapeutic indication and the administration route, as well as the age and weight of the patient.

The following examples illustrate the preparation of the compounds of formula (I) and of the intermediates of formulae (II) and (IV).

A - Example of the preparation of a compound of formula (II).

5 **Preparation of methyl 2-cyclohexylmethylamino-5-methoxybenzoate**

17.6 g of methyl 5-methoxyanthranilate, 11.8 ml of cyclohexanecarboxaldehyde and 2 g of 10% palladium-on-charcoal (50% water) are charged to 200 ml of methanol in a 1 litre hydrogenation apparatus.

The apparatus is placed under a hydrogen atmosphere and
10 agitated at room temperature for 3 hours.

300 ml of dichloromethane are added, the palladium-on-charcoal is separated off by filtration and the filtrate obtained is concentrated under vacuum.

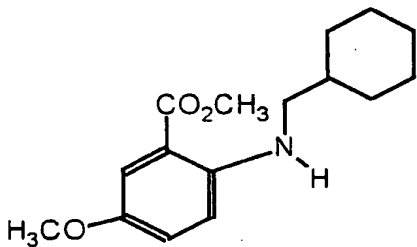
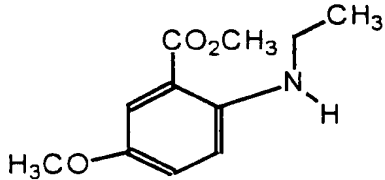
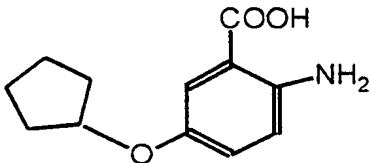
The oil obtained crystallizes from an ethanol (200 ml) and water (50 ml) mixture to give 25.4 g of a yellow solid which melts at 58-60°C.

15 IR: (KBr) 1683 cm^{-1} (C=O), 1528 cm^{-1} (C=O)

^1H NMR: (CDCl_3 , 200 MHz) δ ppm: 1.06-1.64 (11H, m, cyclohexyl), 2.93 (2H, t, CH_2), 3.68 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 6.56 (1H, d, phenyl proton), 6.96 (1H, dd, phenyl proton), 7.34 (2H, d + s, phenyl proton + NH).

The formulae and characteristics of the compounds of formula (II)
20 have been combined in Table I.

8
TABLE I

Compound	Structure	
1		M.p. in °C (Köfler) 58-60
2		¹ H NMR (200 MHz) CDCl ₃ δ PPM Oil 1.28 (t, 3H) 3.20 (q, 2H) 3.77 (s, 3H) 3.88 (s, 3H) 6.71 (d, 1H) 7.09 (dd, 1H) 7.28 (s, 1H) 7.50 (d, 1H)
3		M.p. in °C (Köfler) 147-149

5 **B - Example of the preparation of a compound of formula (IV).**

Preparation of 4-chloro-2-(chloroacetamido)benzoic acid

25.5 ml of chloroacetyl chloride are added dropwise with stirring to 50 g of 2-amino-4-chlorobenzoic acid in 600 ml of dioxane, the reaction mixture being maintained at 20°C.

10 Stirring is then maintained for 2 hours at room temperature and then 1200 ml of water are added. The desired product precipitates, the mixture is stirred for one hour and then filtered and the solid obtained is washed with water.

After drying, 60.7 g of 4-chloro-2-(chloroacetamido)benzoic acid are obtained, the melting point of which is 194-196°C.

IR: 1676 cm^{-1} (C=O)

^1H NMR: (d_6 -DMSO, 200 MHz) δ ppm: 4.30 (2H, s, CH_2), 7.1 (1H, d, phenyl proton), 7.7 (1H, d, phenyl proton), 8.5 (1H, s, phenyl proton), 11.75 (1H, s, NH), 13.90 (1H, broad s, COOH).

The formulae and characteristics of the compounds of formula (IV) have been combined in Table II.

10

TABLE II

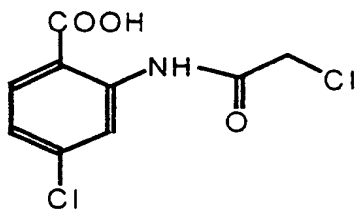
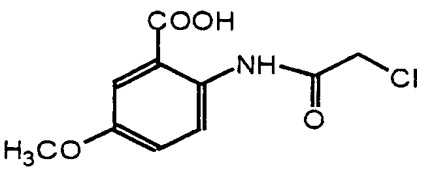
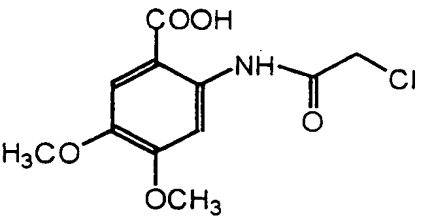
Compound	Structure	M.p. in ° C (Köfler)
1		194-196
2		182-184
3		236-238

TABLE II (continuation)

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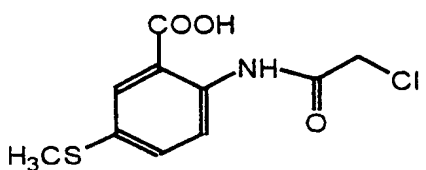
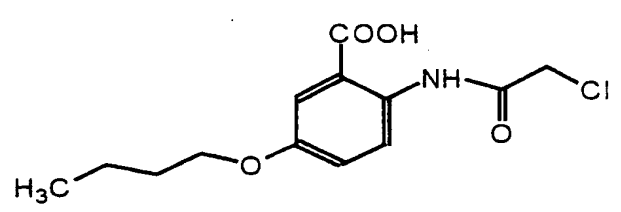
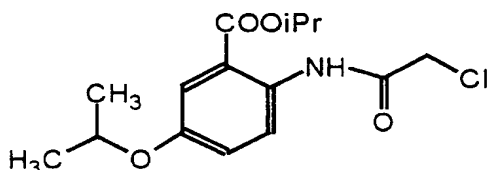
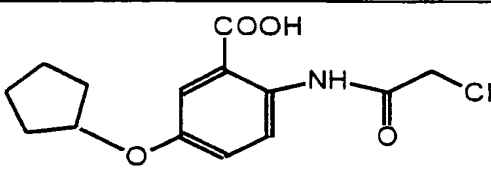
Compound	Structure	M.p. in ° C (Köfler)
4		180-182
5		155-157
6		83-85
7		217-219

TABLE II (continuation)

Compound	Structure	¹ H NMR (200 MHz) CDCl ₃ δ ppm
8		Oil 0.99 (t, 3H) 3.35 (m, 1H) 3.63 (d, 2H) 3.89 (s+m, 7H) 7.12 (m, 2H) 7.40 (d, 1H)
9		Oil 1.05 (t, 3H) 1.57 (m, 6H) 2.81 (dd, 1H) 3.66 (s, 2H) 3.81 (s, 6H) 3.88 (dd, 1H) 7.13 (m, 2H) 7.38 (d, 1H)

5 **C - Example of the preparation of a compound of formula (II)**

Preparation of 4-chloro-2-{[4-(2-methoxyphenyl)-1-piperazinyl]acetamido} benzoic acid

15 g of 4-chloro-2-(chloroacetamido)benzoic acid are added, with stirring and at room temperature, to 11.6 g of 1-(2-methoxyphenyl)piperazine and
 10 17 ml of triethylamine in 120 ml of DMF.

The reaction mixture is kept stirring for 48 hours at room temperature and then 500 ml of water are added. Extraction is carried out with 3 × 300 ml of dichloromethane. The solvent is evaporated under vacuum and the solid thus obtained is taken up again in 300 ml of a 2N aqueous sodium
 15 hydroxide solution. The solution is washed with 3 × 200 ml of diethyl ether and the aqueous phase is then acidified with acetic acid.

A solid crystallizes to give, after filtration, 22.5 g of crude product. After recrystallization from dioxane, 21.1 g of 4-chloro-2-{[4-(2-methoxyphenyl)-

1-piperazinyl]acetamido}benzoic acid are obtained in the form of a white solid which melts at 218-220°C.

IR: 1699 cm^{-1} (C=O), 1673 cm^{-1} (C=O)

^1H NMR: (CF_3COOD), δ ppm: 4.25 (3H, s, OCH_3), 4.65 (8H, broad s, 4 CH_2), 4.95 (2H, s, CH_2), 7.5 (2H, m, phenyl protons), 7.6 (1H, d, phenyl proton), 7.90 (2H, m, phenyl protons), 8.50 (1H, d, phenyl proton), 8.75 (1H, s, phenyl proton).

D - Alternative form of the preparation of a compound of formula (I)

10 Preparation of 2-{[4-(4-fluorophenyl)-1-piperazinyl]-acetamido}-4,5-(methylenedioxy)benzoic acid

15 15 g of 2-(chloroacetamido)-4,5-(methylenedioxy)benzoic acid are added, with stirring and at room temperature, to 10.5 g of 1-(4-fluorophenyl)piperazine and 16.2 ml of triethylamine in 150 ml of DMF.

The reaction mixture is kept stirring for 48 hours at room temperature.

3.5 ml of acetic acid are added and 150 ml of water are slowly added. The acid crystallizes and is diluted with 300 ml of water. The mixture is stirred for 30 minutes and filtered and the solid obtained is washed with water.

20 After recrystallization from a dioxane/DMF mixture, 14.9 g of 2-{[4-(4-fluorophenyl)-1-piperazinyl]acetamido}-4,5-(methylenedioxy)benzoic acid are obtained, which product melts at 254-256°C.

IR (KBr): 1654 cm^{-1} (C=O)

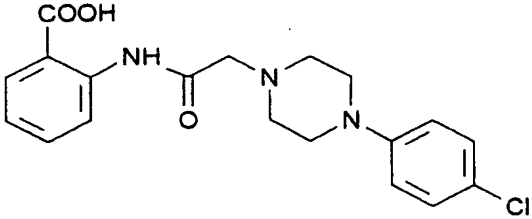
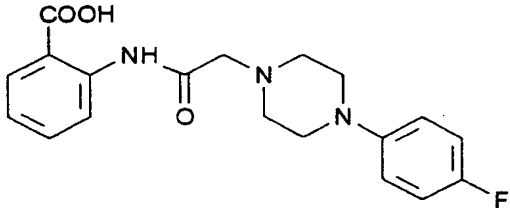
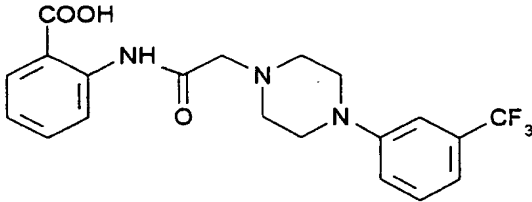
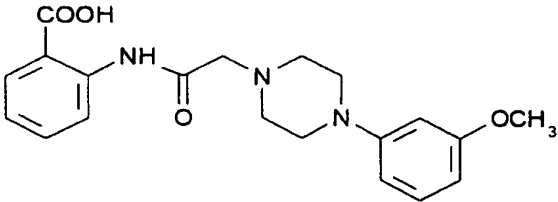
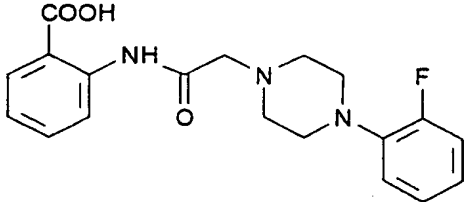
^1H NMR: (CF_3COOD , 200 MHz) δ ppm: 4.40 (8H, s, piperazinyl), 4.67 (2H, s, CH_2), 6.05 (2H, s, $\text{O}-\text{CH}_2-\text{O}$), 7.30 (2H, t, phenyl proton), 7.65 (3H, m, phenyl proton), 7.90 (1H, s, phenyl proton).

The formulae and characteristics of compounds of formula (I) have been combined in Table III.

TABLE III

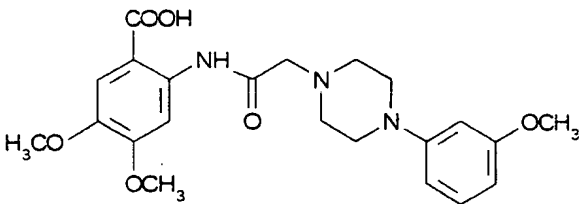
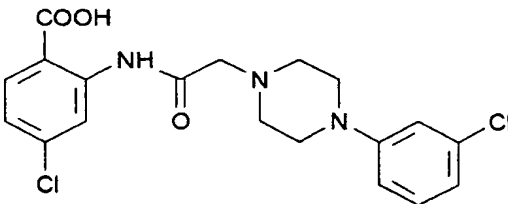
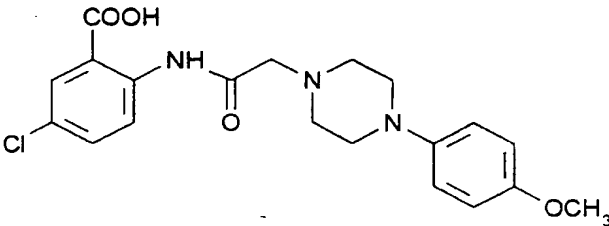
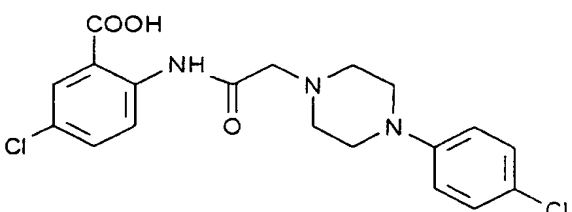
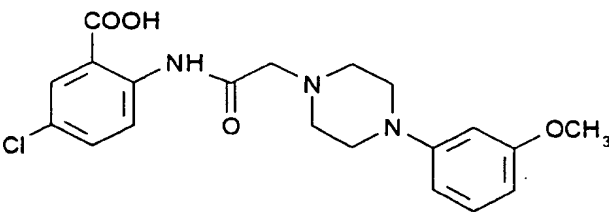
Compound	Structure	M.p. in °C (Köfler)	¹ H NMR (200 MHz) δ ppm
1		185-187	d6-DMSO 2.60 (s, 4H) 3.10 (s, 4H) 3.20 (s, 2H) 3.70 (s, 3H) 6.80 (q, 4H) 7.10 (t, 1H) 7.55 (t, 1H) 8 (d, 1H) 8.7 (d, 1H)
2		233-235	CF ₃ COOD 4.25 (s, 8H) 4.65 (s, 2H) 7.30 (t, 1H) 7.55 (s, 5H) 7.70 (t, 1H) 8.25 (m, 2H)
3		248-250	CF ₃ COOD 4.25 (s, 8H) 4.55 (s, 2H) 7.10 (d, 1H) 7.50 (s, 5H) 8.05 (d, 1H) 8.30 (s, 1H)
4		241-243	CF ₃ COOD 4 (s, 3H) 4.5 (s, 8H) 4.8 (s, 2H) 7.2 (d, 2H) 7.4 (d, 1H) 7.65 (d, 2H) 8.25 (d, 1H) 8.60 (s, 1H)
5		> 265	CF ₃ COOD 4.20 (s, 8H) 4.62 (s, 2H) 7.20 (d, 1H) 7.55 (s, 4H) 8.10 (d, 1H) 8.35 (s, 1H)

Compound	Structure	M.p. in °C (Köfler)	¹ H NMR (200 MHz) δ ppm
6		199-201	CF ₃ COOD 3.8(s,3H) 4.25(s,8H) 4.60(s,2H) 7.20(m,4H) 7.5(m,1H) 8.15(d,1H) 8.40(s,1H)
7		238-240	CF ₃ COOD 4.60(d,8H) 4.90(s,2H) 7.50(m,3H) 7.85(m,2H) 8.35(d,1H) 8.65(s,1H)
8		244-246	CF ₃ COOD 4.10(s,8H) 4.45(s,2H) 7.05(d,3H) 7.45(m,2H) 7.95(d,1H) 8.20(s,1H)
9		191-193	CF ₃ COOD 4.25(d,8H) 4.60(s,2H) 7.15(d,1H) 7.75(m,4H) 8.10(d,1H) 8.30(s,1H)
10		218-220	CF ₃ COOD 4.25(s,3H) 4.65(s,8H) 4.95(s,2H) 7.5(m,2H) 7.6(d,1H) 7.9(m,2H) 8.5(d,1H) 8.75(s,1H)

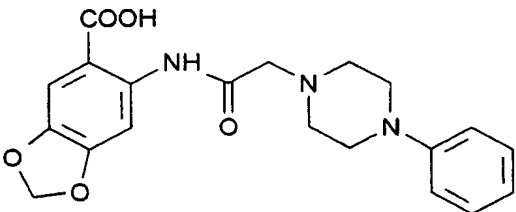
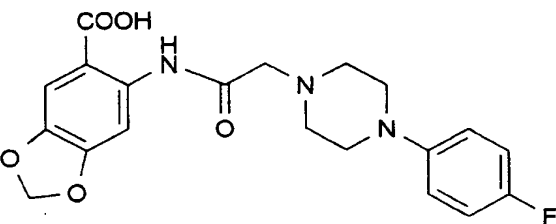
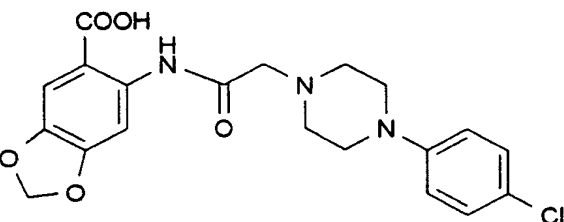
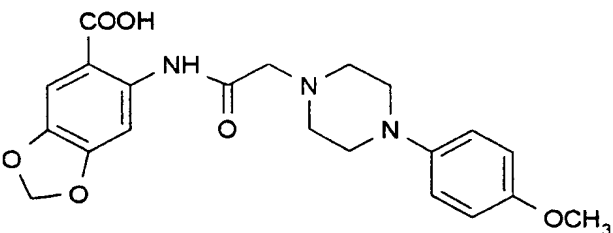
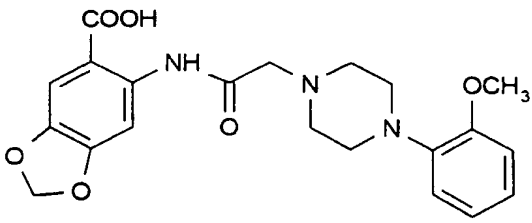
Compound	Structure	M.p. in °C (Köfler)	¹ H NMR (200 MHz) δ ppm
11		260-262	CF ₃ COOD 4.3(s,8H) 4.7(s,2H) 7.25(t,1H) 7.55(s,4H) 7.70(t,1H) 8.25(m,2H)
12		249-251	CF ₃ COOD 4.2(s,8H) 4.6(s,2H) 7.2(m,3H) 7.6(m,3H) 8.15(m,2H)
13		174-176	CDCl ₃ 2.65(s,4H) 3.10(s,2H) 3.20(s,4H) 7.00(m,7H) 8.65(d,1H) 10.00(s,1H) 11.8(s,1H)
14		190-192	CF ₃ COOD 3.85(s,3H) 4.30(s,8H) 4.75(s,2H) 7.5(m,6H) 8.15(t,2H)
15		169-171	CDCl ₃ 2.74(s,3H) 3.15(s,8H) 3.20(s,2H) 6.80(m,5H) 7.5(t,1H) 7.75(d,1H) 8.80(d,1H) 11.45(s,1H) 12.00(s,1H)

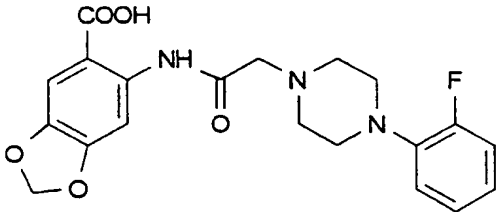
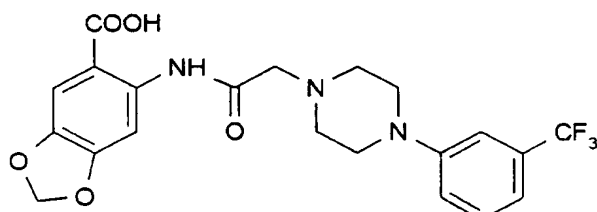
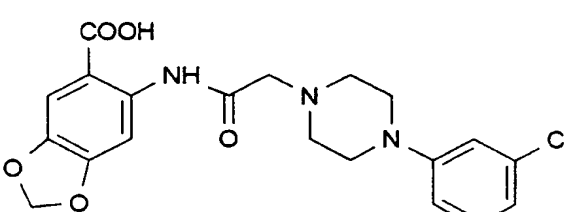
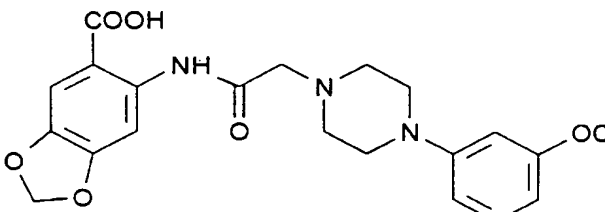
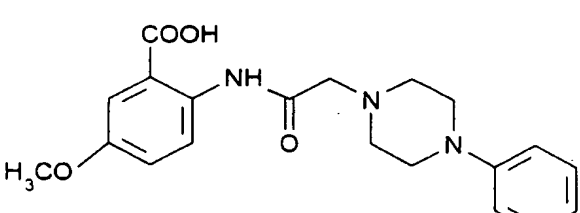
Compound	Structure	M.p. in °C (Köfler)	¹ H NMR (200 MHz) δ ppm
16		217-219	CDCl ₃ 3.5(s,3H) 3.75(s,8H) 4.29(s,2H) 6.65(d,2H) 6.85(t,1H) 7.10(m,3H) 7.75(t,2H)
17		190-192	CF ₃ COOD 3.75(s,8H) 4.15(s,2H) 6.75(m,1H) 7.00(m,5H) 7.60(m,2H)
18		>265	CF ₃ COOD 3.65(s,6H) 4.15(s,8H) 4.5(s,2H) 7.55(s,5H) 7.65(s,1H) 7.85(s,1H)
19		>265	CF ₃ COOD 3.75(s,6H) 4.15(s,8H) 4.50(s,2H) 7.05(t,2H) 7.42(m,2H) 7.55(s,1H) 7.85(s,1H)
20		>265	CF ₃ COOD 3.80(s,6H) 4.15(s,8H) 4.50(s,2H) 7.40(s,4H) 7.60(s,1H) 7.90(s,1H)

Compound	Structure	M.p. in °C (Köfler)	¹ H NMR (200 MHz) δ ppm
21		246-248	CF ₃ COOD 3.75(s,3H) 3.85(s,6H) 4.15(s,8H) 4.50(s,2H) 6.90(d,2H) 7.40(d,2H) 7.60(s,1H) 7.95(s,1H)
22		244-246	CF ₃ COOD 3.80(s,9H) 4.25(s,8H) 4.50(s,2H) 7.00(d,2H) 7.40(d,2H) 7.60(s,1H) 7.95(s,1H)
23		245-247	CF ₃ COOD 3.80(s,6H) 4.20 + 4.35(2s,8H) 4.50(s,2H) 7.20(q,2H) 7.50(m,3H) 7.95(s,1H)
24		255-257	CF ₃ COOD 3.75(s,6H) 4.10+4.20(2s,8H) 4.50(s,2H) 7.60(m,5H) 7.85(s,1H)
25		>265	CF ₃ COOD 3.80(s,6H) 4.15(s,8H) 4.50(s,2H) 7.35(m,4H) 7.55(s,1H) 8.85(s,1H)

Compound	Structure	M.p. in °C (Köfler)	¹ H NMR (200 MHz) δ ppm
26		255-257	CF ₃ COOD 3.70(s,3H) 3.85(s,6H) 4.22(s,8H) 4.50(s,2H) 6.95(s,3H) 7.35(t,1H) 7.55(s,1H) 7.88(s,1H)
27		257-259	CF ₃ COOD 4.15+4.17(2s,8H) 4.50(s,2H) 7.10(d,1H) 7.40(m,4H) 8.00(d,1H) 8.25(s,1H)
28		239-241	CF ₃ COOD 3.70(s,3H) 4.10(s,8H) 4.50(s,2H) 6.90(d,2H) 7.30(d,2H) 7.40(d,1H) 8.00(s,1H) 8.10(d,1H)
29		>265	CF ₃ COOD 4.15(s,8H) 4.55(s,2H) 7.40(s+d,5H) 8.00(s,1H) 8.15(d,1H)
30		199-201	CF ₃ COOD 3.85(s,3H) 4.30(s,8H) 4.65(s,2H) 7.15(m,3H) 7.55(m,2H) 8.15(s,1H) 8.30(d,1H)

Compound	Structure	M.p. in °C (Köfler)	¹ H NMR (200 MHz) δ ppm
31		262-264	CF ₃ COOD 4.30+4.50(2s,8H) 4.67(s,2H) 7.30(m,2H) 7.65(m,3H) 8.15(s,1H) 8.25(d,1H)
32		245-247	CF ₃ COOD 4.05(s,8H) 4.40(s,2H) 7.05(t,2H) 7.40(d,3H) 7.90(s,1H) 8.05(d,1H)
33		213-215	CF ₃ COOD 4.25+4.40(2s,8H) 4.70(s,2H) 7.55(d,1H) 7.80(m,4H) 8.15(s,1H) 8.25(d,1H)
34		203-205	CF ₃ COOD 3.80(s,3H) 4.20(s,8H) 4.45(s,2H) 6.95(d,2H) 7.42(q,3H) 8.05(s+d,2H)
35		224-226	CF ₃ COOD 4.10(s,8H) 4.45(s,2H) 7.40(m,5H) 7.95(s,1H) 8.10(d,1H)

Compound	Structure	M.p. in °C (Köfler)	¹ H NMR (200 MHz) δ ppm
36		238-240	CF ₃ COOD 4.20(s,8H) 4.50(s,2H) 5.85(s,2H) 7.45(s,6H) 7.80(s,1H)
37		254-256	CF ₃ COOD 4.40(s,8H) 4.67(s,2H) 6.05(s,2H) 7.30(t,2H) 7.65(m,3H) 7.90(s,1H)
38		>265	CF ₃ COOD 4.22(s,8H) 4.57(s,2H) 5.92(s,2H) 7.52(s,5H) 7.80(s,1H)
39		236-238	CF ₃ COOD 3.83(s,3H) 4.25(s,8H) 4.59(s,2H) 6.0(s,2H) 7.13(d,2H) 7.49(t,3H) 7.82(s,1H)
40		257-259	CF ₃ COOD 3.97(s,3H) 4.29(s,8H) 4.59(s,2H) 6.06(s,2H) 7.15(d,2H) 7.55(s,3H) 7.82(s,1H)

Compound	Structure	M.p. in °C (Köfler)	¹ H NMR (200 MHz) δ ppm
41		236-238	CF ₃ COOD 4.23+4.38(2s,8H) 4.56(s,2H) 5.97(s,2H) 7.31(m,2H) 7.55(m,3H) 7.76(s,1H)
42		228-230	CF ₃ COOD 4.05+4.15(2s,8H) 4.35(s,2H) 5.75(s,2H) 7.30(s,1H) 7.60(m,5H)
43		240-242	CF ₃ COOD 4.00(s,8H) 4.37(s,2H) 5.75(s,2H) 7.35(d,5H) 7.70(s,1H)
44		198-200	CF ₃ COOD 3.55(s,3H) 4.00(s,8H) 4.30(s,2H) 5.71(s,2H) 6.85(s,3H) 7.25(s,2H) 7.60(s,1H)
45		188-190	CF ₃ COOD 4.05(s,3H) 4.42(s,8H) 4.78(s,2H) 7.45(d,1H) 7.72(s,5H) 7.93(s,1H) 8.30(d,1H)

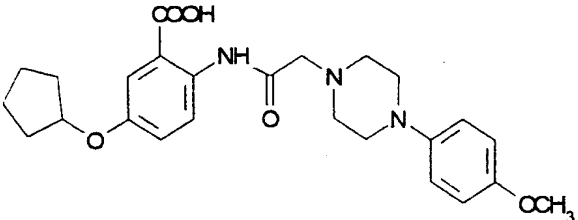
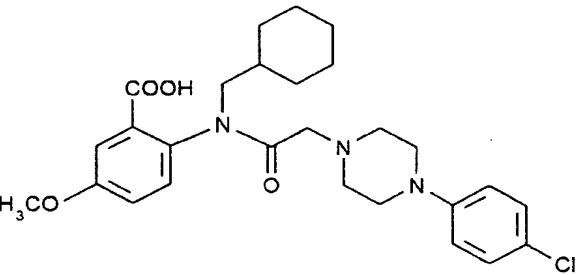
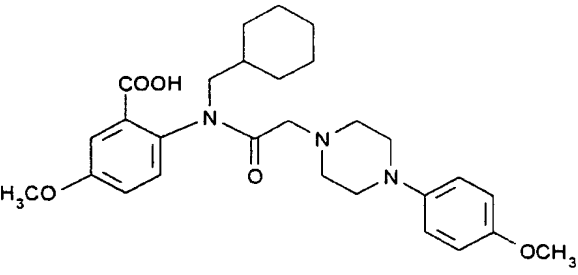
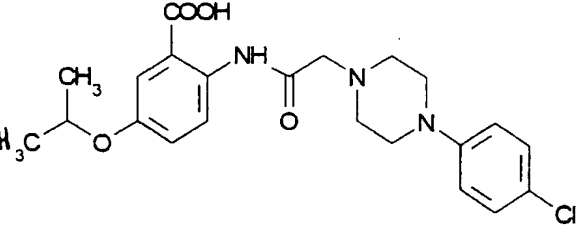
Compound	Structure	M.p. in °C (Köfler)	¹ H NMR (200 MHz)
46		197-199	CF ₃ COOD 3.75(s,3H) 4.20(s,8H) 4.50(s,2H) 7.10(m,3H) 7.50(t,2H) 7.70(s,1H) 8.05(d,1H)
47		221-223	CF ₃ COOD 3.80(s,3H) 4.20(s,8H) 4.55(s,2H) 7.15(d,1H) 7.40(s,4H) 7.70(s,1H) 8.00(d,1H)
48		198-200	CF ₃ COOD 3.85(d,6H) 4.25(s,8H) 4.75(s,2H) 7.22(s,2H) 7.40(s,1H) 7.58(s,2H) 7.82(s,1H) 8.20(s,1H)
49		171-173	CF ₃ COOD 3.75(s,3H) 4.15(s,8H) 4.50(s,2H) 7.15(s,1H) 7.70(d,5H) 8.05(s,1H)

Compound	Structure	M.p. in °C (Köfler)	¹ H NMR (200 MHz)
50		200-202	CF ₃ COOD 3.65(s,3H) 3.70(s,3H) 4.12(s,8H) 4.42(s,2H) 7.00(d,2H) 7.10(d,1H) 7.40(m,2H) 7.65(s,1H) 8.00(d,1H)
51		179-181	CF ₃ COOD 3.72(s,3H) 4.25(d,8H) 4.50(s,2H) 7.15(m,3H) 7.50(q,2H) 7.65(d,1H) 8.00(d,1H)
52		177-179	CF ₃ COOD 3.88(s,3H) 3.96(s,3H) 4.34(s,8H) 4.72(s,2H) 7.20(m,1H) 7.39(dd,1H) 7.62(m,1H) 7.88(s,1H) 8.22(d,3H)
53		182-184	CF ₃ COOD 3.95(s,3H) 4.40(s,8H) 4.70(s,2H) 7.30(d,1H) 7.60(m,3H) 7.85(s,1H) 8.25(d,1H)

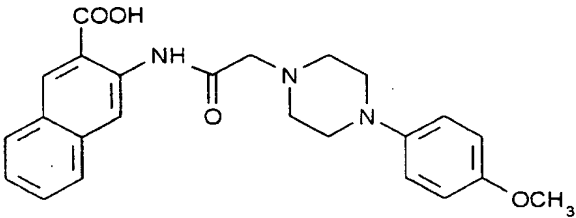
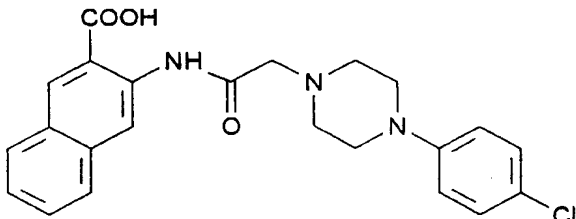
Compound	Structure	M.p. in °C (Köfler)	¹ H NMR (200 MHz)
54		210-212	d ₆ -DMSO 2.42(d,4H) 2.90(s,2H) 3.10(s,4H) 3.18(s,3H) 6.80(t,1H) 6.93(d,2H) 7.25(t,2H) 7.50(m,2H) 7.70(t,1H) 8.00(d,1H)
55		226-227	d ₆ -DMSO 2.34(d,4H) 2.81(s,2H) 3.00+3.10(2s,7H) 6.93(d,2H) 7.22(d,2H) 7.47(m,2H) 7.70(d,1H) 7.95(d,1H)
56		193-195	d ₆ -DMSO 2.55(d,4H) 3.03(s,2H) 3.25(d,7H) 7.25(m,3H) 7.60(m,3H) 7.82(t,1H) 8.12(d,1H)
57		208-210	d ₆ -DMSO 2.55(s,4H) 3.00(d,6H) 3.25(s,3H) 3.80(s,3H) 7.00(s,4H) 7.65(m,2H) 7.82(d,1H) 8.10(d,1H)

Compound	Structure	M.p. in °C (Köfler)	¹ H NMR (200 MHz)
58		196-198	d ₆ -DMSO 2.15(s,4H) 2.65(s,2H) 2.80(s,4H) 2.90(s,3H) 3.55(s,3H) 6.20(t,3H) 6.85(t,1H) 7.25(m,2H) 7.50(d,1H) 7.75(d,1H)
59		144-145	d ₆ -DMSO 2.55(s,4H) 2.95(s,6H) 3.20(s,3H) 3.90(s,3H) 7.00(d,4H) 7.60(m,2H) 7.80(d,1H) 8.10(d,1H)
60		189-191	CF ₃ COOD 2.38(s,3H) 3.77(s,3H) 4.22(s,8H) 4.60(s,2H) 7.05(d,2H) 7.50(d,3H) 8.07(s,1H) 8.15(d,1H)
61		214-216	d ₆ -DMSO 2.50(s,3H) 2.83(s,4H) 3.39(2s,6H) 7.05(d,2H) 7.43(d,2H) 7.66(dd,1H) 7.96(s,1H) 8.79(d,2H) 12.20(s,1H) 13.80(s,1H)

Compound	Structure	M.p. in °C (Köfler)	¹ H NMR (200 MHz)
62		167-169	d ₆ -DMSO 0.75(t,3H) 1.24(m,2H) 1.58(q,2H) 2.52(s,4H) 2.94(s,6H) 3.50(s,3H) 3.81(t,2H) 6.71(q,4H) 7.05(dd,1H) 7.28(s,1H) 8.45(d,1H) 11.77(s,1H) 13.43(s,1H)
63		159-161	d ₆ -DMSO 0.83(t,3H) 1.32(m,2H) 1.58(q,2H) 2.60(s,4H) 3.16+3.32(2s,6H) 3.88(t,2H) 6.87(d,2H) 7.10(d,3H) 7.35(d,1H) 8.60(d,1H) 11.81(s,1H) 13.50(s,1H)
64		187-189	d ₆ -DMSO 1.62(m,8H) 2.64(s,4H) 3.20+3.28(2s,6H) 4.75(s,1H) 6.86(d,2H) 7.13(m,3H) 7.39(s,1H) 8.56(d,1H) 10.15(s,1H)

Compound	Structure	M.p. in °C (Köfler)	¹ H NMR (200 MHz)
65		171-173	d ₆ -DMSO 1.51(m,8H) 2.52(s,4H) 2.98(s,6H) 3.50(s,3H) 4.60(s,1H) 6.60(q,4H) 6.98(dd,1H) 7.28(s,1H) 8.45(d,1H) 11.77(s,1H) 13.43(s,1H)
66		236-238	d ₆ -DMSO 1.35(m,11H) 2.56(s,4H) 2.84(m,3H) 3.12(s,4H) 4.90(s+m,4H) 6.92(d,2H) 7.28(m,4H) 7.46(d,1H)
67		209-211	d ₆ -DMSO 1.00(m,5H) 1.66(m,6H) 2.49(s,4H) 2.90(m,7H) 3.73(s,3H) 3.85(s+m,4H) 6.83(q,4H) 7.24(q,2H) 7.40(s,1H)
68		218-220	d ₆ -DMSO 1.54(d,6H) 3.00(s,4H) 3.50(s,6H) 4.67(m,1H) 7.05(d,2H) 7.35(d,3H) 7.74(d,1H) 8.98(s,1H) 12.00(s,1H)

Com- pound	Structure	M.p. in °C (Köfler)	¹ H NMR (200 MHz)
69		132-134	d ₆ -DMSO 1.20(d,6H) 2.79(s,4H) 3.13(s,4H) 3.20(s,2H) 3.62(s,3H) 4.37(m,1H) 4.94(s,1H) 6.60(d,2H) 6.79(d,2H) 7.00(dd,1H) 7.43(s,1H) 8.56(d,1H) 11.88(s,1H)
70		161-163	d ₆ -DMSO 1.05(t,3H) 2.50(s,4H) 3.00(s,2H) 3.20(s,5H) 3.92(m+s,4H) 6.94(d,2H) 7.28(m,4H) 7.47(s,1H) 13.62(s large,1H)
71		150-152	CF ₃ COOD 3.58 s , 3.79 s , 18H 3.92 m , 6.83(d,2H) 7.10(s,2H) 7.28(d,2H) 7.58(s,1H)

Compound	Structure	M.p. in °C (Köfler)	¹ H NMR (200 MHz)
72		261-263	CF ₃ COOD 3.90(s,3H) 4.41(s,8H) 4.75(s,2H) 7.13(d,2H) 7.45(m,4H) 7.88(m,2H) 8.64(s,1H) 8.90(s,1H)
73		> 265	CF ₃ COOD 4.40(s,8H) 4.77(s,2H) 7.67(s+m,6H) 7.92(m,2H) 8.68(s,1H) 8.92(s,1H)

Results of the pharmacological studies will be given hereinbelow.

5

Study of the anti-diabetic activity in the NOSTZ rat

The anti-diabetic activity of the compounds of formula (I) by the oral route was determined with respect to an experimental model of non-insulin-dependent diabetes induced in the rat by streptozotocin.

The non-insulin-dependent diabetes model is obtained in the rat by a neonatal (the day of birth) injection of streptozotocin.

The diabetic rats used are 8 weeks old. The animals are kept, from the day of their birth to the day of the experiment, in an animal house at a temperature regulated from 21 to 22°C and subject to a fixed cycle of light (from 7 h to 19 h) and of darkness (from 19 h to 7 h). Their feeding consisted of a maintenance diet, water and food was supplied "ad libitum", except for fasting for 2 hours before the test when the food is withdrawn (post-absorptive state).

The rats are treated orally during the day with the test product. Two hours after the final administration of the product and 30 minutes after anaesthetizing the animals with sodium pentobarbital (Nembutal[®]), a 300 µl blood sample is taken from the end of the tail.

5 The main results obtained are combined in Table IV. These results show the effectiveness of the compounds of formula (I) in decreasing glycaemia in the diabetic animals.

These results are expressed as percentage of change in glycaemia at D4 (4 days of treatment) in comparison with D0 (before treatment).

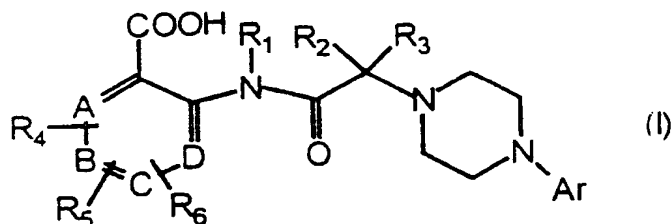
10

TABLE IV

Compound	20 mg/kg/d	200 mg/kg/d
	% Glycaemia at D4	% Glycaemia at D4
35	-12	-16
38	-6	-27
39	-15	-14
45	-9	-18
47	-16	-32
48	-20	-31
50	-17	-7
52	-14	-21

31
CLAIMS

1. A compound selected from the compounds of the formula (I):



5 in which:

Ar is selected from

- mono-, bi- or tricyclic aryl having from 6 to 14 carbon atoms,
- a heteroaromatic group selected from the pyridyl, pyrimidinyl, pyrrolyl, furyl, thienyl, quinolyl, indolyl, benzothienyl, benzofuryl, benzopyranyl, benzothiopyranyl, dibenzofuryl, carbazolyl and benzothiazinyl groups,

10 it being possible for the Ar group to carry 1 to 3 substituents selected from C₁-C₈ alkyl, (C₃-C₈)cycloalkyl(C₁-C₆)alkyl, C₁-C₈ alkoxy, (C₃-C₈)cycloalkyloxy(C₁-C₆)alkyl, (C₃-C₈)cycloalkyl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₃-C₈)cycloalkyloxy, (C₃-C₈)cycloalkyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, C₆-C₁₄ aryl, C₆-C₁₄ heteroaryl, (C₆-C₁₄)heteroaryl(C₁-C₆)alkyl, (C₆-C₁₄)aryl(C₁-C₆)alkyl, (C₆-C₁₄)aryl(C₁-C₆)alkyl(C₆-C₁₄)aryl, (C₆-C₁₄)aryloxy, (C₆-C₁₄)aryloxy(C₁-C₆)alkyl, (C₆-C₁₄)aryl(C₁-C₆)alkyloxy, (C₆-C₁₄)aryl(C₁-C₆)alkyloxy(C₁-C₆)alkyl, halogen, trifluoromethyl, trifluoromethoxy, cyano, hydroxy, nitro, amino, carboxy, (C₁-C₆)alkoxycarbonyl, carbamoyl, (C₁-C₈)alkylthio, (C₁-C₈)alkylsulphinyl, (C₁-C₈)alkylsulphonyl, sulphoamino, (C₁-C₈)alkylsulphonylamino, sulphamoyl and (C₁-C₈)alkylcarbonylamino, or two of these substituents forming methylenedioxy, 4-carboxyphenyl and substituted 4-carboxyphenyl being excluded from the definition of Ar,

R₁, R₂ and R₃ are selected, independently of one another, from:

- hydrogen,
- C₁-C₈ alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl group,

- cycloalkyl containing from 3 to 8 carbon atoms, (C₃-C₈)cycloalkyl(C₁-C₆)alkyl, (C₃-C₈)cycloalkyloxy-(C₁-C₆)alkyl and (C₃-C₈)cycloalkyl(C₁-C₆)alkoxy(C₁-C₆)-alkyl,

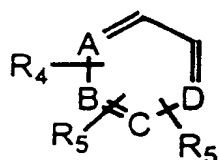
- C₆-C₁₄ aryl, C₆-C₁₄ heteroaryl, (C₆-C₁₄)heteroaryl(C₁-C₆)alkyl, (C₆-C₁₄)aryl(C₁-C₆)alkyl, (C₆-C₁₄)aryl(C₁-C₆)alkyl(C₆-C₁₄)aryl, (C₆-C₁₄)aryl(C₁-C₆)-alkoxy(C₁-C₆)alkyl and (C₆-C₁₄)aryloxy(C₁-C₆)alkyl,

A, B, C and D are =CH- groups, it being possible for one or two of them also to be a nitrogen atom,

R₄, R₅ and R₆ are selected, independently of one another, from:

- hydrogen,
- C₁-C₈ alkyl, (C₃-C₈)cycloalkyl(C₁-C₆)alkyl, C₁-C₈ alkoxy, (C₃-C₈)cycloalkyloxy(C₁-C₆)alkyl, (C₃-C₈)cycloalkyloxy, (C₃-C₈)cycloalkyl(C₁-C₆)alkoxy, (C₃-C₈)cycloalkyl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, C₆-C₁₄ aryl, (C₆-C₁₄)aryl(C₁-C₆)alkyl, (C₆-C₁₄)aryl(C₁-C₆)alkyl(C₆-C₁₄)aryl, (C₆-C₁₄)aryloxy, (C₆-C₁₄)aryloxy(C₁-C₆)alkyl, (C₆-C₁₄)aryl(C₁-C₆)alkoxy, (C₆-C₁₄)aryl(C₁-C₆)alkyloxy(C₁-C₆)alkyl, halogen, trifluoro- methyl, trifluoromethoxy, cyano, carboxyl, hydroxyl, nitro, amino, (C₁-C₆)alkoxycarbonyl, carbamoyl, (C₁-C₆)alkylthio, (C₁-C₈)alkylsulphinyl, (C₁-C₈)alkylsulphonyl, sulphoamino, (C₁-C₈)alkylsulphonylamino, sulphamoyl and (C₁-C₈)alkylcarbonylamino, it being possible for two of these groups to form methylenedioxy or phenyl ring condensed with the ring to which they are attached, it being possible for the various aryl groups to be themselves substituted by 1 to 3 substituents selected from C₁-C₈ alkyl, C₁-C₈ alkoxy, halogen, trifluoromethyl, trifluoromethoxy, hydroxyl, nitro and amino,
- their solvates and their pharmaceutically acceptable salts.

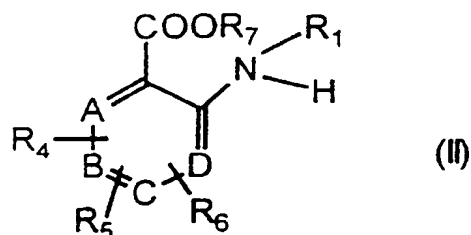
2. A compound as claimed in Claim 1, in which the base component of the ring system



is a phenyl ring.

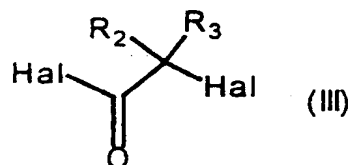
3. A compound as claimed in Claim 2, in which at least one of the R_4 , R_5 and R_6 groups is C_1 - C_8 alkoxy or two of these groups form methylenedioxy.

5 4. A process for the preparation of a compound according to Claim 1, comprising the reaction of an aromatic amine of the formula (II):



in which A, B, C, D, R_1 , R_4 , R_5 and R_6 are as defined above and R_7 is selected from hydrogen, C_1 - C_6 alkyl and benzyl,

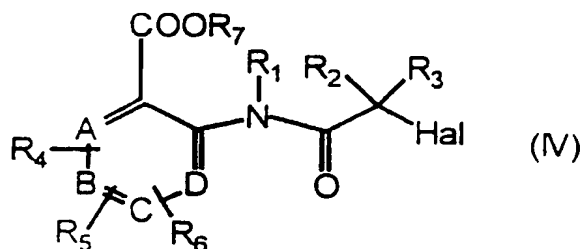
10 with a haloacyl halide of the formula (III):



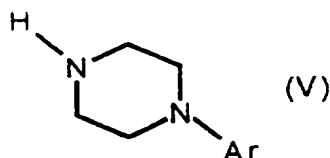
in which R_2 and R_3 are as defined above,

Hal is selected from chlorine and bromine,

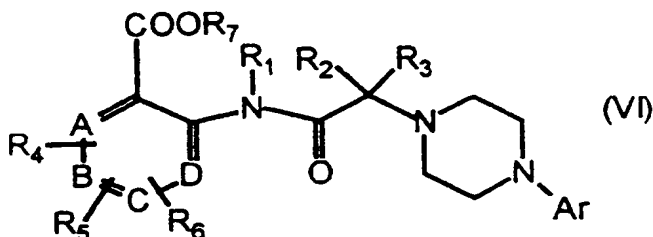
in order to form a compound of the formula (IV):



in which A, B, C, D, R₁, R₂, R₃, R₄, R₅, R₆, R₇ and Hal are as defined above,
and the reaction of the compound of the formula (IV) with a compound of the
formula (V):



5 in which Ar is as defined above,
in the presence of a basic agent, in order to form the compound of the formula
(VI):



10 in which Ar, A, B, C, D, R₁, R₂, R₃, R₄, R₅, R₆ and R₇ are as defined
above,

and, in the case where R₇ is alkyl, the hydrolysis of this compound
in order to form a compound of formula (I),

and, in the case where R₇ is benzyl, the hydrogenolysis of this
compound in order to form a compound of formula (I).

15 5. A pharmaceutical composition comprising an effective amount of a
compound as claimed in Claim 1.

6. A pharmaceutical composition comprising an effective amount of a
compound as claimed in Claim 2.

7. A pharmaceutical composition comprising an effective amount of a
20 compound as claimed in Claim 3.

8. A method for the treatment of diabetes which comprises
administering to a human in need thereof an effective amount of a compound as
claimed in Claim 1.

9. A method for the treatment of diabetes which comprises administering to a human in need thereof an effective amount of a compound as claimed in Claim 2.

10. A method for the treatment of diabetes which comprises
s administering to a human in need thereof an effective amount of a compound as claimed in Claim 3.

INTERNATIONAL SEARCH REPORT

Inte I Application No
PCT/EP 98/03431

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D295/15 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 98 27078 A (MERCK PATENT GMBH) 25 June 1998 see claims 1-4	1-10
A	FR 2 693 722 A (LES LABORATOIRES MERAM S.A.) 21 January 1994 see claims 1-9	1-10
A	EP 0 638 568 A (ADIR ET COMPAGNIE) 15 February 1995 see claims 1-13	1-10
A	BE 850 709 A (LABORATOIRE L. LAFON) 16 May 1977 see claims 1-3	1-10
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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- "O" document referring to an oral disclosure, use, exhibition or other means
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Date of the actual completion of the international search

29 January 1999

Date of mailing of the international search report

05/02/1999

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INTERNATIONAL SEARCH REPORT

Inte : Application No
PCT/EP 98/03431

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 96 26924 A (SUNTORY LTD.) 12 February 1997 see claims 1-13</p> <p>-----</p>	1-10

INTERNATIONAL SEARCH REPORT

information on patent family members

Inte : Application No
PCT/EP 98/03431

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